Hepatol Int (2007) 1:343–354
DOI 10.1007/s12072-007-9011-8

ORIGINAL PAPER

Current and novel therapies for the treatment of nonalcoholic steatohepatitis

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Received: 30 May 2007 / Published online: 26 July 2007

Abstract The worldwide epidemic of obesity and the metabolic syndrome has made nonalcoholic fatty liver disease (NAFLD), one of the most important liver diseases of our time. NAFLD is now the commonest cause of abnormal liver test results in industrialized countries and its incidence is rising. The current treatment of nonalcoholic steatohepatitis (NASH) has focused on lifestyle modification to achieve weight loss and modification of risk factors, such as insulin resistance, dyslipidemia, and hyperglycemia associated with the metabolic syndrome. With our increasing understanding of the pathogenesis of NASH, have come a plethora of new pharmacologic options with great potential to modify the natural history of NAFLD and NASH. This article focuses on a number of novel molecular targets for the treatment of NASH as well as the evidence for currently available therapy. It should be noted, however, that in part because of the long natural history of NASH and NAFLD, no therapy to date has been shown to unequivocally alter liver-related morbidity and mortality in these patients.

Keywords Peroxisome proliferator-activated receptors · Cannabinoid system · Incretins · Adiponectin · Leptin · Metabolic liver disease · Angiotensin receptor blockers

Introduction

The worldwide epidemic of obesity and the metabolic syndrome has made nonalcoholic fatty liver disease (NAFLD) a part of the spectrum of disorders that includes hepatic steatosis, nonalcoholic steatohepatitis (NASH), and cirrhosis, one of the most important liver diseases of our time. NAFLD is now the commonest cause of abnormal liver test results in industrialized countries and its incidence is rising, approaching 30% in some populations [1, 2]. In the United States, 12–15% of the population has NAFLD (~45 million people), while 3–4% have NASH [3]. The startling rise of obesity and type II diabetes in the Asia Pacific region suggests that similarly high levels there are not far off [4]. In the past, NASH was considered a benign entity. However, it is now appreciated that NASH can cause progressive fibrosis in a proportion of affected individuals [5], and is responsible for the majority of cases of cryptogenic cirrhosis [6]. The long-term prognosis is no better than that of hepatitis C cirrhosis and the majority of patients with NASH-related cirrhosis succumb to liver related causes [7]. In persons with NAFLD and the absence of cirrhosis, morbidity from cardiovascular disease and type 2 diabetes is high.

NAFLD is strongly linked to overweight and obesity with the majority of patients having features of the metabolic syndrome [8, 9]. In case series, between 70% and 80% of patients with NASH are obese, 50–70% are hypertensive, and up to 70% have dyslipidemias [10, 11]. In many respects, therefore, NAFLD can be considered the hepatic manifestation of the metabolic syndrome [12]. The pathophysiological process that ties these conditions together is insulin resistance, which is now considered to be an intrinsic defect in NAFLD [13]. According to the two-hit theory of NAFLD [14], insulin resistance is the initiating event that causes an increase in hepatic triacylglyceride synthesis and steatosis [15]. In turn, insulin resistance per se is proinflammatory and in conjunction with other pathophysiological processes operating in a fatty

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liver provides the so-called second or additional hit(s). These processes, including oxidative stress, mitochondrial damage, proinflammatory cytokine release, inadequate cellular defenses, and immune-mediated and host genetic factors, lead to hepatic injury (hepatitis) and fibrosis [16].

Owing to the lack of large randomized trials, the current treatment of NASH has focused on lifestyle modification to achieve weight loss, and modification of risk factors, such as insulin resistance, dyslipidemia, and hyperglycemia associated with the metabolic syndrome. With an increasing understanding of the pathogenesis of NASH have come a plethora of new pharmacologic options with great potential to modify its natural history (see Tables 1–4). Many of these agents target insulin resistance, while others target the additional hits such as oxidative stress, cytokine-induced inflammation, or fibrosis itself (see Fig. 1). This article focuses on a number of novel molecular targets for the treatment of NASH, as well as the evidence for currently available therapy. It should be noted, however, that in part because of the long natural history of NASH and NAFLD, no therapy to date has been shown to unequivocally alter liver-related morbidity and mortality in these patients.

Peroxisome-proliferator-activated receptors

Peroxisome-proliferator-activated receptors (PPARs) are part of the nuclear receptor superfamily that regulates gene expression in response to ligand binding. PPARα, PPARγ, and PPARδ have been identified to date and all play a role in the regulation and coordination of lipid and carbohydrate metabolism [39]. A summary of the effects of PPAR receptors can be found in Table 2.

PPARγ agonists

Thiazolidenediones

Expression of PPARγ is highest in adipose tissue, but is also found in vascular endothelium, pancreatic beta cells, liver, and macrophages [40, 41]. The primary effect of PPARγ activation is an increase in the number and differentiation status of subcutaneous adipocytes. This results in increased fatty acid uptake by adipocytes, sparing the liver, skeletal muscle, and pancreatic beta cells from the harmful metabolic effects of lipotoxicity [42, 43]. Other beneficial effects include an increase in plasma adiponectin levels [44] and adiponectin receptor expression in the liver. The overall effect of PPARγ activation is thus an increase in insulin sensitivity and glycemic control, coupled with a reduction in circulating free fatty acids. For this reason, PPARγ agonists theoretically address and can reverse the main pathophysiological abnormality present in NASH.

The thiazolidenediones (troglitazone, rosiglitazone, and pioglitazone) were first discovered to be ligands for the PPARγ receptor in 1995 and subsequently have been shown to be highly effective insulin-sensitizing agents in a number of large studies [45, 46]. Unfortunately, their metabolic improvements are generally accompanied by weight gain and an increase in subcutaneous fat [47, 48]. A pilot study of troglitazone in NASH [49] was promising,

Table 1 Potential molecular targets for NASH

Therapeutic target/class	Examples	Status as NASH therapy
Peroxisome-proliferator-activated receptor ligands		
PPARγ agonists	Rosiglitazone, pioglitazone, troglitazone	Phase III clinical trials
PPARα agonists	Clofibrate, gemfibrozil	Phase II clinical trials
PPARα/γ agonists	Muraglitazar, tesaglitazar, naveglitazar, netoglitazone	Phase II clinical trials, some preclinical
Renin-angiotensin system		
Angiotensin receptor blockers	Irbesartan, losartan, telmisartan	Phase III clinical trials
Adipocytokines	Adiponectin, leptin	Preclinical
Cannabinoid system		
CB1 antagonist	Rimonabant	Phase III clinical trials
Biguanides	Metformin	Phase III clinical trials
HMG-CoA reductase inhibitors	Pravastatin, atorvastatin, rosuvastatin	Phase III clinical trials
Incretins	Exenatide, liraglutide	Preclinical
Antioxidants and hepatoprotective agents	Vitamin E, Vitamin C, betaine, pentoxifylline, probucol, *N*-acetylcysteine, ursodeoxycholic acid	Phase II and III clinical trials
Weight loss agents	Silbutramine, orlistat	Phase II clinical trials

Table 2 Effects of activation of PPAR receptors

PPAR receptor	Sites of high expression	Physiological actions	Net effect of activation
PPARγ	Adipose tissue	↑ FA trapping subcutaneously	↓ Plasma FAs
	Liver, immune cells	↑ Glucose uptake by muscle	↑ Insulin sensitivity
		↑ Adiponectin levels and receptors	↑ Glycemic control
		↑ Subcutaneous fat mass	Weight gain
PPARα	Liver	↑ FA oxidation	↓ Plasma TGs
	Skeletal muscle	↑ TG hydrolysis	↑ Plasma HDL
	Kidney, heart	↓ VLDL particles	
	Immune cells	Inhibition of cytokines IL6, COX-2	Anti-inflammatory
PPARδ	Adipose tissue	↑ FA transport and oxidation	↓ Plasma TGs
	Skeletal muscle (10–50 × more than other PPARs)	↑ HDL production	↑ Plasma HDL
	Liver	↑ Thermogenesis	Weight loss
		↓ Glucose production	↑ Glycemic control
			↑ Insulin sensitivity

Abbreviations: PPAR, peroxisome proliferator activated receptor; FA, fatty acid; TG, triglyceride; VLDL, very low density lipoprotein; HDL, high-density lipoprotein

Table 3 Major pharmacotherapy trials in NASH

Drug	Study type	No.	Duration (months)	Control	Biochemical improvement	Histological improvement	Adverse events	References
Rosiglitazone	Open label	30	12	–	Yes	Yes: in S and I	Weight gain 6 kg	Neuschwander-Tetri [17]
Pioglitazone	RCT	55	6	Diet	Yes	Yes: in S and I	Weight gain 2 kg	Belfort [18]
Pioglitazone and vitamin E	RCT	20	6	Vitamin E	Yes	Yes: in S and I	No	Sanyal [19]
Clofibrate	Open label	16	12	–	No	No improvement	No	Laurin [20]
Losartan	Open label	7	12	–	Yes	Yes: in I and F	No	Yokohama [21]
Rimonabant	RCT	1036	12	Placebo	Yes	Not biopsied	Anxiety, nausea	Despres [22]
Atorvastatin	Open label	25	12	–	Yes	Not biopsied	No	Gomez-Dominguez [23]
Pravastatin	Open label	5	6	–	Yes	Yes: in S and I	No	Rallidis [24]
Metformin	RCT	36	6	Diet	Yes	No improvement	No	Uygun [25]
Metformin	RCT	110	12	Vitamin E or diet	Yes	Yes: in S and I	No	Bugianesi [26]

Abbreviations: I: inflammation; F: fibrosis; S: steatosis; RCT: randomized controlled trail

with normalization of liver enzymes in the majority of patients, after 6 months. Only modest beneficial changes in histology were noted. However, a causal link to a number of cases of severe hepatotoxicity [50, 51] led to troglitazone being withdrawn in March 2000. In a subsequent open-label trial of 30 overweight patients with NASH, rosiglitazone (4 mg twice daily) for 48 weeks demonstrated significant improvements in liver biochemistry and in indices of insulin resistance [17]. Importantly, in almost half the patients with repeat biopsy, there were such marked reductions in steatosis and necroinflammatory scores that they no longer met histological criteria for a diagnosis of NASH. Improvements in pericellular fibrosis, but not in fibrosis stage, were also noted. The major adverse event was weight gain with a mean increase of over 6 kg, which persisted in the 6-month post-trial follow-up. In another

Table 4 Antioxidant and hepatoprotective medication trials in NASH

Drug	Study type	No.	Duration (months)	Control	Biochemical improvement	Histological improvement	Adverse events	References
Vitamin E	Open label	22	12	Diet	Variable	Yes: mild	No	Hasegawa [27]
Vitamin E and C	RCT	49	6	Placebo	No	Yes: in F, No change in I	No	Harrison [28]
Vitamin E and ursodeoxycholic acid	RCT	48	2	Placebo, Urso	Yes	Yes: in S and I	No	Dufour [29]
Betaine	Case series	10	12	–	Yes	Yes: in S, F, and I	Nausea, cramps	Abdelmalek [30]
Silybin and Vitamin E	Open label	85	6	HCV	Yes	Not biopsied	No	Loguercio [31]
Ursodeoxycholic acid	RCT	166	24	Placebo	No	No improvement	No	Lindor [32]
Probucol	RCT	30	6	Placebo	Yes	Not biopsied	No	Merat [33]
Silbutramine	Open label	13	6	Orlistat	Yes	Not biopsied	Raised ALP	Sabuncu [34]
Orlistat	Case series	14	6	–	Yes	Yes: in S, F, and I	No	Hussein [35]
N-Acetylcysteine	Open label	35	1	–	No	Not biopsied	No	Pamuk [36]
Pentoxifylline	Open label	20	12	–	Yes	Not biopsied	Severe nausea	Adams [37]
Pentoxifylline	Open label	9	12	–	Yes	Yes: in S, F and I	No	Satapathy [38]

Abbreviations: I: Inflammation; F: fibrosis; S: steatosis; RCT: randomized controlled trail; Urso: ursodeoxycholic acid; ALP: alkaline phosphatase, HCV; hepatitis C virus

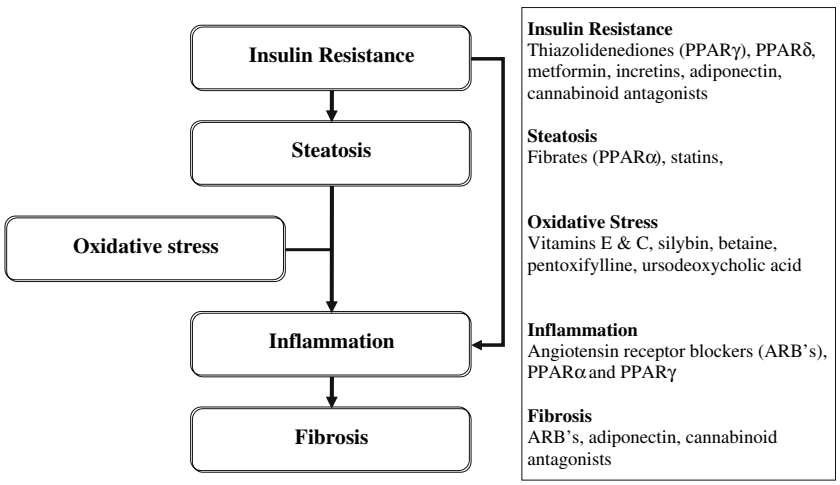

Fig. 1 Pathogenesis of NASH and predominant sites of drug action

controlled trial, pioglitazone and vitamin E was compared to vitamin E alone in 20 patients with NASH [19]. At the 6-month follow-up, all patients had significant improvements in liver biochemistry, but post-treatment histology in the vitamin E group demonstrated only a minor reduction in steatosis. The pioglitazone group had reduced inflammation, pericellular fibrosis, and a significant further reduction in steatosis. No weight gain was seen in either group.

In a more recent controlled trial, 55 patients with NASH were randomized to a hypocaloric diet plus pioglitazone 45 mg/d or diet and placebo for 6 months [18]. When compared to controls, those in the pioglitazone-treated group showed a marked improvement in insulin resistance, HbA1c, and normalization of liver enzymes. Significant decreases in circulating TNF and elevations in adiponectin levels were noted. On histological evaluation, reductions in

steatosis and necroinflammatory scores were significant in the pioglitazone group compared to controls. There was no significant change in the fibrosis stage, however, with pioglitazone treatment, possibly because of the short duration of follow-up. Again, weight gain was the principal adverse effect, with a mean increase of over 2 kg. Larger trials of longer duration are currently underway to assess the long-term benefits and safety of these agents.

PPARα agonists

Fibrates

PPARα receptors are most prominently expressed in the liver, kidney, heart, and skeletal muscle [52] and can be activated by eicosanoids, free fatty acids, and drugs of the fibrate class [53]. Activation results in increased uptake and oxidation of free fatty acids, increased triglyceride hydrolysis and upregulation of ApoA-I and ApoA-II. The net effect is fatty acid oxidation, decrease in serum triglycerides, a rise in high-density lipoprotein (HDL) levels, and an increase in cholesterol efflux [54]. PPARα activation also has anti-inflammatory effects via inhibition of COX2, IL-6, and CRP [55]. PPARα is also downregulated in hepatitis C with steatosis [56] and in mice models of NAFLD [57], suggesting a possible antisteatotic role.

Trials of fibrates in human NASH, however, have been unimpressive. In a pilot series, 12 months' treatment with clofibrate in 16 patients with NASH and elevated triglycerides had no impact on liver enzyme elevation or triglyceride levels. Likewise, histological improvement was not noted [20]. Gemfibrozil improved transaminases irrespective of initial triglyceride level in one subsequent 4-week study [58], but larger trials of these agents have not eventuated because of interest in other potentially more promising therapies. Data are emerging for the use of bezafibrate (a novel fibrate with pan PPAR agonist actions) with promising results seen in tamoxifen-induced NASH [59] and in the methionine-choline–deficient mouse model of NASH [60]. Larger trials are needed.

Dual PPARα/γ agonists

Dual PPARα/γ agonists are very attractive as therapy for NASH and the metabolic syndrome, as they have the potential to improve insulin resistance, reduce circulating free fatty acids, and avoid the weight gain associated with thiazolidenediones. A number of such agents have recently been developed, including muraglitazar, tesaglitazar, naveglitazar, and netoglitazone [61]. In early trials, these agents reduced levels of circulating triglycerides, increased HDL levels, and improved insulin sensitivity [62–64]. An amelioration in the PPARγ-mediated weight gain via a PPARα-associated decrease in food intake and lipid oxidation has been demonstrated in animals [62, 65], but these results are yet to be replicated in humans. Safety concerns have led to the recent withdrawal of muraglitazar and tesaglitazar from phase III trails owing to an increased incidence of heart failure and elevations in serum creatinine levels, respectively [66]. Pan-PPAR agonists and dual agonists involving PPARδ remain in preclinical development. Finding the correct balance in receptor-binding affinity is the target of ongoing research to ensure high efficacy and a good safety profile [61].

PPARδ

The PPARδ appears to be a powerful metabolic regulator, with actions on fat, skeletal muscle, liver, and the heart. Its activation enhances fatty acid transport and oxidation, improves glucose homeostasis via inhibition of hepatic glucose output, turns off macrophage inflammatory responses, and dramatically increases circulating HDL levels. Thus, selective PPARδ agonists (currently in development) have the potential to target multiple components of the metabolic syndrome, including obesity, dyslipidemia, hyperglycemia, insulin resistance, and possibly NASH [67].

Renin-angiotensin system

Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers

At present, no accepted therapy that exists can delay or reverse the hepatic fibrosis associated with NASH or other fibrotic liver diseases. Transforming growth factor β1 (TGF-β1) plays a dominant role in the development of fibrosis [68] and is known to be upregulated by angiotensin II [69]. Animal studies have demonstrated that angiotensin II is crucial for the development of hepatic fibrosis [70], and that its blockade via either ACE inhibitors [71] or angiotensin receptor blockers (ARBs) [72] reduces fibrosis and inflammation. In a pilot study, seven patients with NASH were treated for 12 months with the ARB losartan (50 mg/d), resulting in a significant decrease in plasma levels of TGF-β1, an improvement in liver enzymes and reductions in fibrosis and inflammatory scores on repeat biopsy [21]. A follow-up report demonstrated that the number of activated hepatic stellate cells were dramatically decreased in the losartan-treated patients and these cells were likely a crucial mediator of the drug's effect [73]. Certain ARBs, such as telmisartan, may have additional benefits in the treatment of NASH owing to their ability to block adipocyte differentiation [74] and to improve lipid

metabolism and insulin resistance via partial activation of PPARγ receptors [75] and stimulation of the adiponectin gene [76]. Further large trials of both ACE inhibitors and ARBs in NASH are currently underway.

Cannabinoid modulators

CB1 antagonists

The endocannabinoid (EC) system comprising short-lived endocannabinoid agonists, and their protein-coupled receptors CB1 and CB2, have recently been discovered to play a role in the mediation of hepatic fibrosis, as well as in the regulation of body weight, energy, and lipid homeostasis [22, 77]. Cannabinoid agonists, such as delta-9-tetrahydrocannibinol (THC), have a wide range of effects including psychoactivation, stimulation of food intake, analgesia, antiemesis [78], and possibly anti-inflammatory and antitumor effects [79]. Cannabinoid receptors are most prominent in the brain (CB1) and immune system (CB2), but have recently been discovered on hepatocytes and hepatic myofibroblasts [80, 81]. CB1 receptors are upregulated in advanced cirrhosis and experiments in mice have shown that use of CB1 antagonists can prevent diet-induced fatty liver and obesity, decrease de novo fatty acid synthesis [82], and decrease the fibrotic response to both acute and chronic liver injury [83]. CB2 receptors on the other hand appear to be antifibrogenic [81]; however, the observation that daily cannabis smoking is an independent risk factor for fibrosis progression in hepatitis C [84] suggests that the profibrogenic CB1 response is dominant.

In adipocytes, stimulation of the CB1 receptor promotes lipogenesis and inhibits adiponectin [85]. Rimonabant, the first CB1 antagonist in clinical use, alters the metabolic activity of adipose tissue, induces adiponectin production, and reduces food intake and body weight [86]. In obese humans, 1 year's treatment with 20 mg rimonabant was associated with an 8.6-kg weight loss, a 9.1-cm reduction in waist circumference, a 23% mean increase in HDL levels, and a 15% mean decrease in triglyceride levels. There was also a 58% increase in plasma adiponectin and an improvement in insulin resistance [22]. CB1 antagonism, therefore, is a promising treatment for obesity, the metabolic syndrome, and NASH.

Adipocytokines

Adiponectin

Adiponectin is secreted by adipocytes and circulates as both low- and high-molecular-weight multimers, with the high-molecular-weight multimers appearing to be responsible for its insulin-sensitizing and anti-inflammatory properties [87, 88]. Two receptors, AdipoR1 and AdipoR2—located predominantly in muscle cells and the liver, respectively—mediate the actions of adiponectin [89]. PPARγ is involved in transcriptional upregulation and activation of the adiponectin gene, and the PPARγ agonist thiazolidenediones increase serum adiponectin levels [90]. Adiponectin stimulates PPARα and lipid oxidation, reduces hepatic triglycerides, and has anti-inflammatory effects via inhibition of macrophages and blockade of TNF release [91]. Serum adiponectin levels have been found to correlate inversely with body mass index (BMI), body fat, fasting insulin concentrations, and serum triglyceride levels [92]. Not surprisingly, hypoadiponectinemia appears to have a strong association with NASH and is predictive of more advanced grades of steatosis and necroinflammation, independent of insulin resistance [93].

Proof of therapeutic potential of adiponectin has been demonstrated in a number of animal studies. In isolated hepatic stellate cells, adiponectin attenuates liver fibrosis via decreased TGF-β1 and connective tissue growth factor (CTGF) expression [94], while in a separate study adiponectin appeared to prevent hepatic injury via a reduction in TNF release [95]. In contrast, adiponectin knockout mice demonstrate enhanced hepatic fibrosis in response to hepatotoxic insults [88]. In *ob/ob* mice, adiponectin treatment is associated with improvements in steatosis, liver enzyme levels, and hepatic inflammation [96]. It should also be noted that several of the drugs reviewed in this article, including the thiazolidenediones [90], cannabinoid antagonists [86], and angiotensin receptor blockers [76] are thought to exert part of their beneficial effects via an increase in plasma adiponectin levels.

The main obstacle to the use of adiponectin as therapy for NASH and the metabolic syndrome lies in the fact that it is a protein that requires parenteral administration. However, it is likely that a better understanding of the precise molecular mechanisms of adiponectin action will result in small-molecule mimetics that can be administered orally. Similar agents such as the receptor tyrosine kinase inhibitors have revolutionized the treatment of diseases such as chronic myeloid leukemia [97] and gastrointestinal stromal tumors [98]. Thus, it is very likely that adiponectin or agents that mimic the actions of adiponectin will be evaluated in future as a therapy for NASH [99].

Leptin

After its discovery in 1994 as the *ob* gene product, leptin was considered to be an anorexigenic hormone with the potential to both decrease food intake and increase energy expenditure [99]. The hope that it would be a panacea for

obesity was short-lived when it became clear that despite its deficiency causing obesity in mice, in humans most obese persons had elevated leptin levels in association with leptin resistance [100]. Leptin has subsequently been shown to be a mediator of hepatic fibrosis via upregulation of proinflammatory cytokines and stimulation of hepatic stellate cells [101, 102]. Most, but not all, reports have shown an increase in leptin levels in NASH patients when compared to controls [103–105]. While it may not be a target for direct intervention in NASH, a better understanding of its role and its interplay with adiponectin remains of great interest.

Metformin

The biguanide insulin-sensitizing agent metformin has been widely touted as a therapy for NASH owing to its ability to improve hyperinsulinemia and hepatic insulin resistance in the absence of weight gain [106–108]. While the exact mechanism of action remains uncertain, metformin appears to interact primarily with mitochondria, where it stimulates fatty acid oxidation [109], suppresses lipogenic enzymes, and stimulates pyruvate kinase [110, 111]. Initial studies in insulin-resistant *ob/ob* mice with fatty liver were very promising, with resolution of hepatomegaly, steatosis, and biochemical abnormalities [112]. Subsequent human trials have, however, demonstrated variable results. In an open-label study of 15 patients with NASH, metformin (20 mg/kg) treatment was associated with improvements in liver biochemistry and insulin resistance after 3 months. Thereafter, however, there were no improvements in insulin resistance, and liver enzymes gradually rose to pretreatment levels [113]. In another controlled trial, 36 patients with NASH were randomized to treatment with metformin 850 mg twice daily plus a low-calorie diet, or to a control group of diet alone for 6 months [25]. The metformin group achieved significant reductions in liver enzymes, markers of insulin resistance, and BMI when compared with controls, but had no significant improvement in the necroinflammatory grade or fibrosis stage in post-treatment biopsies. A subsequent 12-month trial [26] followed 110 patients with NASH and compared 55 patients treated with metformin 2 g daily to 28 who received vitamin E 400 IU twice daily and to 27 given a prescription low-calorie diet. Patients in the metformin arm had significantly increased rates of liver enzyme normalization and an improvement in all metabolic parameters when compared to controls. A reduction in steatosis and necroinflammatory scores was noted in metformin-treated patients. It should be noted, however, that these improvements were noted only in a selected subgroup and were not compared to either of the controls. Thus, while these results are promising, further clarification on the beneficial effects of metformin for the treatment of NASH is warranted. Currently, three large NIH-funded phase III trials should provide clearer data on the long-term benefits and safety of metformin in nondiabetic patients with NASH.

HMG-CoA reductase inhibitors

Statins

Until recently, the use of statins in patients with liver damage or elevated transaminases has been discouraged both by manufacturers and the US Food and Drug Administration owing to concerns relating to hepatic toxicity. This is despite the overall incidence of liver enzyme elevations being less than 3% in statin registration trials [114], and a recent meta-analysis of almost 50,000 patients from these trials that did not show any significant increase in liver enzyme elevations compared to placebo [115]. A number of studies have now demonstrated the safety of standard doses of atorvastatin, pravastatin, and lovastatin in patients with suspected NAFLD [116, 117]. Overall data on the effectiveness of statins in NASH are lacking, but the results of small pilot studies of atorvastatin [23, 118], pravastatin [24], and rosuvastatin [119] have been encouraging, with normalization of liver enzymes in the majority of patients and improvements in hepatic inflammation and steatosis in some. Further large trials with serial hepatic histology, particularly with fibrosis as an end point, are awaited.

Incretins

Incretin mimetics

Incretins, such as glucagon-like peptide 1 (GLP-1) are gut-derived hormones that stimulate insulin and suppress glucagon secretion, inhibit gastric emptying, and reduce food intake [120]. Incretin mimetics (GLP-1 agonists; exenatide, liraglutide) are given subcutaneously and have been shown in phase III trials to reduce fasting and postprandial glucose, improve insulin sensitivity, and reduce HbA1c [121, 122] and are associated with modest but significant weight loss [123]. Adverse effects such as nausea appear to be mild and transient [121]. The ability of these agents to assist with weight loss and satiety may make them a useful adjunct in diabetic patients with NASH.

Antioxidants and hepatoprotective agents

Much interest has focused on antioxidants given that oxidative stress is thought to be a key pathophysiological

mechanism for the development of necroinflammation in NASH [16]. Vitamin E in particular has been the subject of many studies, with mixed results (see Table 3). No benefit was seen when used alone [27], but in randomized trials with combination vitamin C [28] or ursodeoxycholic acid (a potentially cytoprotective hydrophilic bile acid) [29], histological improvement has been recorded. Despite these results, the long-term use of vitamin E cannot be recommended in light of a recent meta-analysis of vitamin E trails that showed an increase in all-cause mortality [124]. Other agents, such as betaine [30] (a methyl donor and part of the methionine-recycling pathway), probucol [33] (an enterally acting hypolipidemic agent), and pentoxifylline [37] (an oral inhibitor of TNF production), have shown biochemical improvements in small trials, although pentoxifylline caused such severe nausea that almost half the cohort withdrew from treatment. A very recent report of nine patients treated with pentoxifylline demonstrated a significant improvement in liver biochemistry, insulin sensitivity, and histology after 12 months, including a reduction in fibrosis score in four patients. Although uncontrolled, its data suggest there is merit in further studies of this drug. [38]. In contrast, *N*-acetylcysteine [36] (a cysteine donor that is metabolized to the antioxidant glutathione) and ursodeoxycholic acid alone have not been shown to have any benefit.

Weight loss agents

Silbutramine, orlistat

In obese patients with NASH, small open-label trials have shown biochemical and histological improvements associated with significant weight loss using the lipase inhibitor orlistat [34, 35]. Silbutramine has shown similar biochemical improvements in the absence of histology [34], but for both, larger trials are needed to confirm efficacy and safety. They are likely to be a useful adjunct in obese subjects who have failed other weight reduction strategies.

Conclusion

In conclusion, many promising therapies are currently being studied for the treatment of NASH. By and large, these have arisen from a more detailed understanding of the molecular mechanisms that modulate energy homeostasis, lipid metabolism, and insulin sensitivity. In turn, NASH, being the "new kid on the block," has benefited from decades of research on type 2 diabetes, dyslipidemia, and insulin resistance. Through modulation of nuclear receptors, lipogenic enzymes, and adipocytokines, the prospect of effective treatments that address all aspects of the metabolic syndrome including NASH may be just over the horizon. The key challenge with regard to NAFLD and NASH will be the conduct of clinical trials that demonstrate treatment-related improvements in liver-related morbidity, if not mortality. At a population level, however, it must be emphasized that pharmacotherapy for NASH should have as its bedrock effective lifestyle intervention strategies to reduce obesity and insulin resistance and increase physical activity.

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